ORIGINAL ARTICLE

Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

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ABSTRACT

BACKGROUND

Most patients with locally advanced, unresectable, non–small-cell lung cancer (NSCLC) have disease progression despite definitive chemoradiotherapy (chemotherapy plus concurrent radiation therapy). This phase 3 study compared the anti–programmed death ligand 1 antibody durvalumab as consolidation therapy with placebo in patients with stage III NSCLC who did not have disease progression after two or more cycles of platinum-based chemoradiotherapy.

METHODS

We randomly assigned patients, in a 2:1 ratio, to receive durvalumab (at a dose of 10 mg per kilogram of body weight intravenously) or placebo every 2 weeks for up to 12 months. The study drug was administered 1 to 42 days after the patients had received chemoradiotherapy. The coprimary end points were progression-free survival (as assessed by means of blinded independent central review) and overall survival (unplanned for the interim analysis). Secondary end points included 12-month and 18-month progression-free survival rates, the objective response rate, the duration of response, the time to death or distant metastasis, and safety.

RESULTS

Of 713 patients who underwent randomization, 709 received consolidation therapy (473 received durvalumab and 236 received placebo). The median progression-free survival from randomization was 16.8 months (95% confidence interval [CI], 13.0 to 18.1) with durvalumab versus 5.6 months (95% CI, 4.6 to 7.8) with placebo (stratified hazard ratio for disease progression or death, 0.52; 95% CI, 0.42 to 0.65; P<0.001); the 12-month progression-free survival rate was 55.9% versus 35.3%, and the 18-month progression-free survival rate was 44.2% versus 27.0%. The response rate was higher with durvalumab than with placebo (28.4% vs. 16.0%; P<0.001), and the median duration of response was longer (72.8% vs. 46.8% of the patients had an ongoing response at 18 months). The median time to death or distant metastasis was longer with durvalumab than with placebo (23.2 months vs. 14.6 months; P<0.001). Grade 3 or 4 adverse events occurred in 29.9% of the patients who received durvalumab and 26.1% of those who received placebo; the most common adverse event of grade 3 or 4 was pneumonia (4.4% and 3.8%, respectively). A total of 15.4% of patients in the durvalumab group and 9.8% of those in the placebo group discontinued the study drug because of adverse events.

CONCLUSIONS

Progression-free survival was significantly longer with durvalumab than with placebo. The secondary end points also favored durvalumab, and safety was similar between the groups. (Funded by AstraZeneca; PACIFIC ClinicalTrials.gov number, NCT02125461.)

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*A complete list of the investigators of the PACIFIC study is provided in the Supplementary Appendix, available at NEJM.org.

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Approximately one third of patients with non–small-cell lung cancer (NSCLC) have stage III, locally advanced disease at diagnosis.[1] The standard of care for patients with a good performance status and unresectable stage III NSCLC is platinum-based doublet chemotherapy concurrent with radiotherapy (chemoradiotherapy).[2] However, the median progression-free survival among patients who have received chemoradiotherapy is poor (approximately 8 months), and only 15% of patients are alive at 5 years.[1,3] No major advances in the treatment for patients in this context have been made in many years.[3-14]

Durvalumab is a selective, high-affinity, human IgG1 monoclonal antibody that blocks programmed death ligand 1 (PD-L1) binding to programmed death 1 (PD-1) and CD80, allowing T cells to recognize and kill tumor cells.[15-17] An early-phase clinical study involving multiple advanced solid tumors, including stage IIIB or IV NSCLC,[18] showed that durvalumab had encouraging antitumor activity, and this agent was recently approved in the United States for patients with locally advanced or metastatic urothelial carcinoma who had received platinum-based chemotherapy.[19] Given preclinical evidence suggesting that chemotherapy and radiotherapy may up-regulate PD-L1 expression in tumor cells,[20-22] which is a predictive factor for a response to durvalumab, we hypothesized that durvalumab would provide clinical benefit after chemoradiotherapy.

We report results from an interim analysis of the randomized, double-blind, international, phase 3 PACIFIC study comparing durvalumab as consolidation therapy with placebo in patients with stage III, locally advanced, unresectable NSCLC that had not progressed after platinum-based chemoradiotherapy.

Methods

Patients

Eligible patients had histologically or cytologically documented stage III, locally advanced, unresectable NSCLC according to the *Staging Manual in Thoracic Oncology*, version 7, of the International Association for the Study of Lung Cancer.[23] These patients had received two or more cycles (defined according to local practice) of platinum-based chemotherapy (containing etoposide, vinblastine, vinorelbine, a taxane [paclitaxel or docetaxel], or pemetrexed) concurrently with definitive radiation therapy (54 to 66 Gy), in which the mean dose to the lung was less than 20 Gy, the V20 (the volume of lung parenchyma that received 20 Gy or more) was less than 35%, or both. Additional inclusion criteria were no disease progression after this treatment, an age of 18 years or older, a World Health Organization performance status of 0 or 1 (on a 5-point scale in which higher numbers indicate greater disability), an estimated life expectancy of 12 weeks or longer, and completion of the last radiation dose within 1 to 14 days before randomization (after a protocol amendment, this criterion was changed to 1 to 42 days before randomization).

Key exclusion criteria were previous exposure to anti–PD-1 or PD-L1 antibodies; receipt of immunotherapy or an investigational drug within 4 weeks before the first dose (6 weeks for monoclonal antibodies); active or previous autoimmune disease (within the past 2 years) or a history of primary immunodeficiency; evidence of uncontrolled, concurrent illness or ongoing or active infections; unresolved toxic effects of grade 2 or higher (according to the Common Terminology Criteria for Adverse Events [CTCAE]); and grade 2 or higher pneumonitis from previous chemoradiotherapy. Complete eligibility criteria are provided in the protocol, available with the full text of this article at NEJM.org.

Study Design and Treatments

Patients were randomly assigned within 1 to 42 days after chemoradiotherapy in a 2:1 ratio to receive durvalumab at a dose of 10 mg per kilogram of body weight intravenously or matching placebo every 2 weeks as consolidation therapy for up to 12 months. Patients were stratified according to age (<65 vs. ≥65 years), sex, and smoking history (current or former smoker vs. never smoked).

Administration of the study drug commenced after randomization on day 1, once the patient was confirmed to be eligible to participate. The study drug was discontinued if there was confirmed disease progression, initiation of alternative anticancer therapy, unacceptable toxic effects, or withdrawal of consent. Patients could receive the study drug until disease progression (unless they had rapid tumor progression or symptomatic progression requiring urgent intervention) and could receive the drug again if disease control had been achieved at the end of the 12

months but the disease had progressed during follow-up.

END POINTS AND ASSESSMENTS

The coprimary end points were progression-free survival (according to the Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1, as assessed by means of blinded independent central review) and overall survival. Progression-free survival was defined as the time from randomization (which occurred up to 6 weeks after chemoradiotherapy) to the date of the first documented event of tumor progression or death in the absence of disease progression. Overall survival was defined as the time from randomization until death from any cause. Progression-free survival was assessed by the investigators, according to RECIST, version 1.1, as a predefined sensitivity analysis.

The secondary end points were the percentage of patients who were alive without disease progression at 12 and 18 months, the objective response rate, the duration of response, and the time to death or distant metastasis (all assessed by means of blinded independent central review); and overall survival at 24 months, the safety and side-effect profile (graded with the use of the CTCAE, version 4.03), health-related quality of life, pharmacokinetic characteristics, and immunogenicity. Efficacy was assessed every 8 weeks for the first 12 months and every 12 weeks thereafter. All reported efficacy end points are for durvalumab or placebo only (i.e., they were not aggregate end points that included previous chemoradiotherapy).

Patients provided optional archived tumor-tissue samples for PD-L1 testing. However, enrollment was not restricted to any thresholds for the level of PD-L1 expression.

STUDY OVERSIGHT

The study was designed by representatives of the sponsor (AstraZeneca) and academic advisors. All patients provided written informed consent for participation. The study protocol and amendments were approved by relevant ethics committees, and the study was performed in accordance with the International Conference on Harmonisation Guidelines on Good Clinical Practice and the Declaration of Helsinki. All the investigators (listed in the Supplementary Appendix, available at NEJM.org) were responsible for the collection of data. Data analyses were completed by the sponsor. The authors had full access to the data and vouch for the accuracy and completeness of the data and analyses and for the fidelity of the study to the protocol.

The authors signed a confidentiality agreement with the sponsor. All the authors participated in writing the manuscript and provided approval to submit the manuscript for publication. Medical-writing support, including development of the initial draft of the manuscript, was funded by the sponsor.

STATISTICAL ANALYSIS

The study was to be considered positive if either of the two coprimary end points, progression-free or overall survival, was significantly longer with durvalumab than with placebo. Approximately 702 patients were needed for 2:1 randomization to obtain 458 progression-free survival events for the primary analysis of progression-free survival and 491 overall survival events for the primary analysis of overall survival. It was estimated that the study would have a 95% or greater power to detect a hazard ratio for disease progression or death of 0.67 and a 85% or greater power to detect a hazard ratio for death of 0.73, on the basis of a log-rank test with a two-sided significance level of 2.5% for each coprimary end point.

An interim analysis of progression-free survival was planned when approximately 367 events had occurred. At this interim analysis, the hazard ratio for disease progression or death was estimated with the use of the Kaplan–Meier method. Between-group comparisons were performed with the use of the log-rank test, stratified according to age, sex, and smoking history. Sensitivity analyses included assessment of evaluation bias, evaluation-time bias, and attrition bias in the determination of disease progression and adjustment for various covariates in the estimation of the hazard ratio for disease progression or death.

A preplanned analysis of progression-free survival in 35 prespecified subgroups was performed in which hazard ratios and 95% confidence intervals were calculated with the use of an unstratified Cox regression model. There was no multiplicity adjustment because the subgroup analysis was intended to show consistency of the treatment effect.

Response rates were estimated with the use of the Clopper–Pearson method and compared

with the use of Fisher's exact test. Type I error was controlled for the coprimary end points (as described in the Supplementary Appendix) and the key secondary end point (the objective response rate), but not for other secondary end points. Efficacy was assessed in the intention-to-treat population, and safety was assessed in the as-treated population.

In an ongoing analysis, an external independent data and safety monitoring committee is assessing safety. This committee assessed the interim efficacy analyses.

RESULTS

PATIENTS AND TREATMENT

Between May 2014 and April 2016, a total of 709 of 713 patients who underwent randomization (99.4%) received at least 1 dose of study drug as consolidation therapy (473 patients received durvalumab and 236 received placebo) (Fig. S1 in the Supplementary Appendix). Baseline characteristics were well balanced in the two groups (Table 1, and Table S1 in the Supplementary Appendix). The median age of all patients was 64 years, and the majority were men (70.1%) and current or former smokers (91.0%); 45.7% had a squamous histologic type of tumor. The previous use of chemotherapy was also well balanced between the two groups (Table S2 in the Supplementary Appendix); in addition, 25.8% of the patients in the durvalumab group and 28.7% of those in the placebo group had received induction chemotherapy before definitive chemoradiotherapy. The response to previous chemoradiotherapy was similar in the two groups (complete response, 1.9% in the durvalumab group and 3.0% in the placebo group; partial response, 48.7% and 46.8%, respectively).

According to the assessment of archived tumor samples obtained before chemoradiotherapy, PD-L1 expression of 25% or more on tumor cells occurred in 22.3% of patients (24.2% in the durvalumab group and 18.6% in the placebo group) and PD-L1 expression of less than 25% on tumor cells occurred in 41.0% of the patients (39.3% in the durvalumab group and 44.3% in the placebo group); 36.7% of the patients in both groups had unknown PD-L1 status (Table S3 in the Supplementary Appendix). *EGFR* mutations were observed in 6.0% of the patients (6.1% in the durvalumab group and 5.9% in the placebo group), whereas 67.3% of the patients' tumors were *EGFR*-negative or wild-type (66.2% in the durvalumab group and 69.6% in the placebo group). The *EGFR* mutation status was unknown in 27.7% of the patients in the durvalumab group and 24.5% of the patients in the placebo group (Table S3 in the Supplementary Appendix). No significant ($P<0.05$) between-group differences were noted in either PD-L1 expression or *EGFR* mutation status.

As of February 13, 2017 (the data cutoff point for this interim analysis), 371 patients had disease progression (214 in the durvalumab group and 157 in the placebo group). The overall median follow-up was 14.5 months (range, 0.2 to 29.9). The median number of infusions received was 20 (range, 1 to 27) in the durvalumab group and 14 (range, 1 to 26) in the placebo group; 6.3% and 5.1% of the patients, respectively, were still receiving the study drug at the data cutoff point (Table S4 in the Supplementary Appendix). The median relative dose intensity was 100% in each group (range, 29 to 100 in the durvalumab group and 50 to 100 in the placebo group). Serum trough concentrations of durvalumab were similar at weeks 24 and 48 (177.00 and 189.00 μg per milliliter, respectively) (Table S5 in the Supplementary Appendix).

EFFICACY

Median progression-free survival from randomization, as assessed by means of blinded independent central review, was 16.8 months (95% confidence interval [CI], 13.0 to 18.1) with durvalumab versus 5.6 months (95% CI, 4.6 to 7.8) with placebo (stratified hazard ratio for disease progression or death, 0.52; 95% CI, 0.42 to 0.65; two-sided $P<0.001$) (Fig. 1). The 12-month progression-free survival rate was 55.9% (95% CI, 51.0 to 60.4) with durvalumab and 35.3% (95% CI, 29.0 to 41.7) with placebo, and the 18-month progression-free survival rate was 44.2% (95% CI, 37.7 to 50.5) and 27.0% (95% CI, 19.9 to 34.5), respectively. Progression-free survival results were consistent across all prespecified sensitivity analyses (data not shown), including results determined by investigator assessment (stratified hazard ratio, 0.61; 95% CI, 0.50 to 0.76; two-sided $P<0.001$).

A progression-free survival benefit with durvalumab was consistently observed across all prespecified subgroups, as defined according to patient demographic characteristics, baseline clini-

Table 1. Baseline Characteristics, Stratification Factors, and Prior Therapy in the Intention-to-Treat Population.*

Characteristic	Durvalumab (N = 476)	Placebo (N = 237)	Total (N = 713)
Age — yr			
Median	64	64	64
Range	31–84	23–90	23–90
Sex — no. (%)			
Male	334 (70.2)	166 (70.0)	500 (70.1)
Female	142 (29.8)	71 (30.0)	213 (29.9)
Race — no. (%)†			
White	337 (70.8)	157 (66.2)	494 (69.3)
Black	12 (2.5)	2 (0.8)	14 (2.0)
Asian	120 (25.2)	72 (30.4)	192 (26.9)
Disease stage — no. (%)			
IIIA	252 (52.9)	125 (52.7)	377 (52.9)
IIIB	212 (44.5)	107 (45.1)	319 (44.7)
Other‡	12 (2.5)	5 (2.1)	17 (2.4)
WHO performance-status score — no. (%)§			
0	234 (49.2)	114 (48.1)	348 (48.8)
1	240 (50.4)	122 (51.5)	362 (50.8)
Tumor histologic type — no. (%)			
Squamous	224 (47.1)	102 (43.0)	326 (45.7)
Nonsquamous	252 (52.9)	135 (57.0)	387 (54.3)
Smoking status — no. (%)			
Current smoker	79 (16.6)	38 (16.0)	117 (16.4)
Former smoker	354 (74.4)	178 (75.1)	532 (74.6)
Never smoked	43 (9.0)	21 (8.9)	64 (9.0)
Previous radiotherapy — no. (%)¶			
<54 Gy	3 (0.6)	0	3 (0.4)
≥54 to ≤66 Gy	442 (92.9)	217 (91.6)	659 (92.4)
>66 to ≤74 Gy	30 (6.3)	19 (8.0)	49 (6.9)
Previous chemotherapy — no. (%)‖			
Induction	123 (25.8)	68 (28.7)	191 (26.8)
Concurrent with radiation therapy	475 (99.8)	236 (99.6)	711 (99.7)
Best response to previous chemoradiotherapy — no. (%)			
Complete response	9 (1.9)	7 (3.0)	16 (2.2)
Partial response	232 (48.7)	111 (46.8)	343 (48.1)
Stable disease	222 (46.6)	114 (48.1)	336 (47.1)

* The intention-to-treat population included all patients who underwent randomization. Randomization was stratified according to age at randomization (<65 vs. ≥65 years of age), sex, and smoking history (current or former smoker vs. never smoked). There were no significant (P<0.05) between-group differences in the baseline characteristics listed here. Percentages may not total 100 because of rounding or because some categories occurred with very low frequency and therefore are not shown here. A complete listing of baseline characteristics is provided in Table S1 in the Supplementary Appendix.

† Race was reported by the patients.

‡ Patients with other disease stages included 12 patients in the durvalumab group (4 with stage IV, 4 with stage IIB, 3 with stage IIA, and 1 with stage IA) and 5 patients in the placebo group (2 with stage IIB, 1 with stage IIA, and 2 with stage IB).

§ World Health Organization (WHO) performance-status scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating increased disability.

¶ The decision regarding the actual dose was based on investigator or radiologist assessment of each individual patient, resulting in doses that differed from the inclusion criteria. All radiation therapy was administered concurrently with chemotherapy.

‖ Patients may have received previous chemotherapy in more than one context.

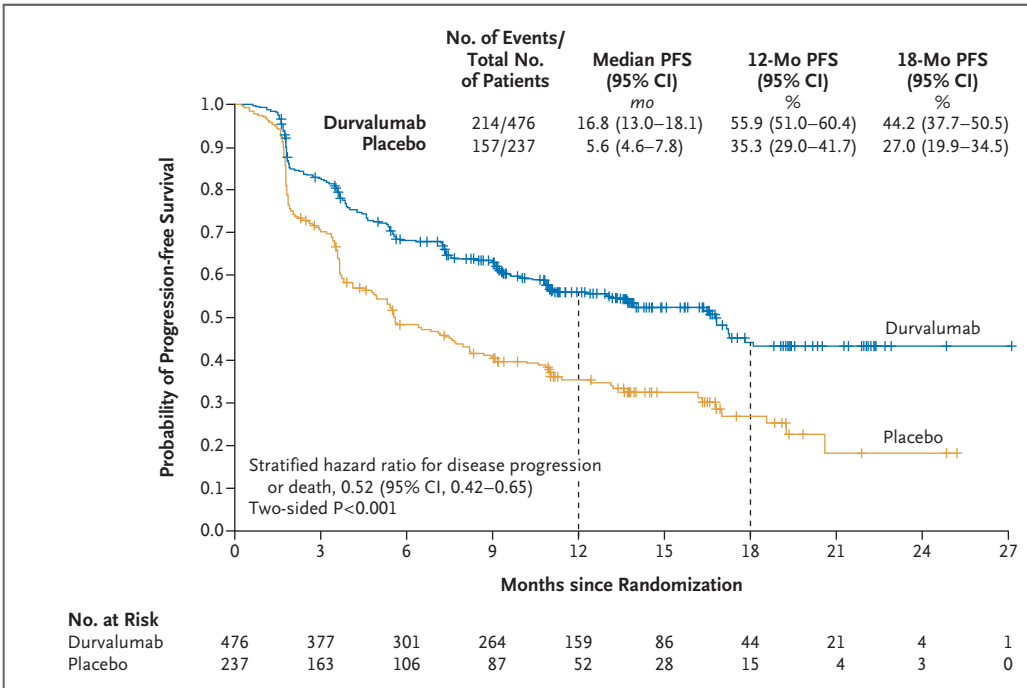

Figure 1. Progression-free Survival in the Intention-to-Treat Population.

Shown are Kaplan–Meier curves for progression-free survival (PFS), defined according to the Response Evaluation Criteria in Solid Tumors, version 1.1, and assessed by means of blinded independent central review. Tick marks indicate censored observations, and vertical lines indicate the times of landmark PFS analyses. The intention-to-treat population included all patients who underwent randomization.

copathologic features, and response to previous treatment (Fig. 2). Additional nonprognostic factors are listed in Figure S2 in the Supplementary Appendix. Notably, the progression-free survival benefit with durvalumab was observed irrespective of PD-L1 expression before chemoradiotherapy (hazard ratio, 0.59 [95% CI, 0.43 to 0.82] for a PD-L1 expression level of <25% and 0.41 [95% CI, 0.26 to 0.65] for a PD-L1 expression level of ≥25%). A progression-free survival benefit was also evident in patients who had never smoked. The absence of corrections for multiple comparisons limits the extrapolations to particular subgroups.

The median time to death or distant metastasis was 23.2 months (95% CI, 23.2 to not reached) with durvalumab versus 14.6 months (95% CI, 10.6 to 18.6) with placebo (hazard ratio, 0.52; 95% CI, 0.39 to 0.69; two-sided P<0.001) (Fig. S3 in the Supplementary Appendix). In addition, the frequency of new lesions, as assessed by means of blinded independent central review, was 20.4% with durvalumab and 32.1% with placebo, with a lower incidence of new brain metastases with durvalumab (5.5% vs. 11.0%) (Table S6 in the Supplementary Appendix).

The objective response rate, as assessed by means of blinded independent central review, was significantly higher with durvalumab than with placebo (28.4% vs. 16.0%; P<0.001) (Table 2); 16.5% of patients who received durvalumab and 27.7% of those who received placebo had disease progression (Table 2). The median duration of response was longer with durvalumab than with placebo (Table 2, and Fig. S4 in the Supplementary Appendix). Of the patients who had a response to durvalumab, 72.8% had an ongoing response at both 12 and 18 months as compared with 56.1% and 46.8%, respectively, of patients in the placebo group who had an ongoing response (Table 2). An analysis of overall survival was not planned at the time of this interim analysis of progression-free survival.

SAFETY

Adverse events of any cause and grade occurred in 96.8% of the patients who received durvalumab and 94.9% of the patients who received placebo

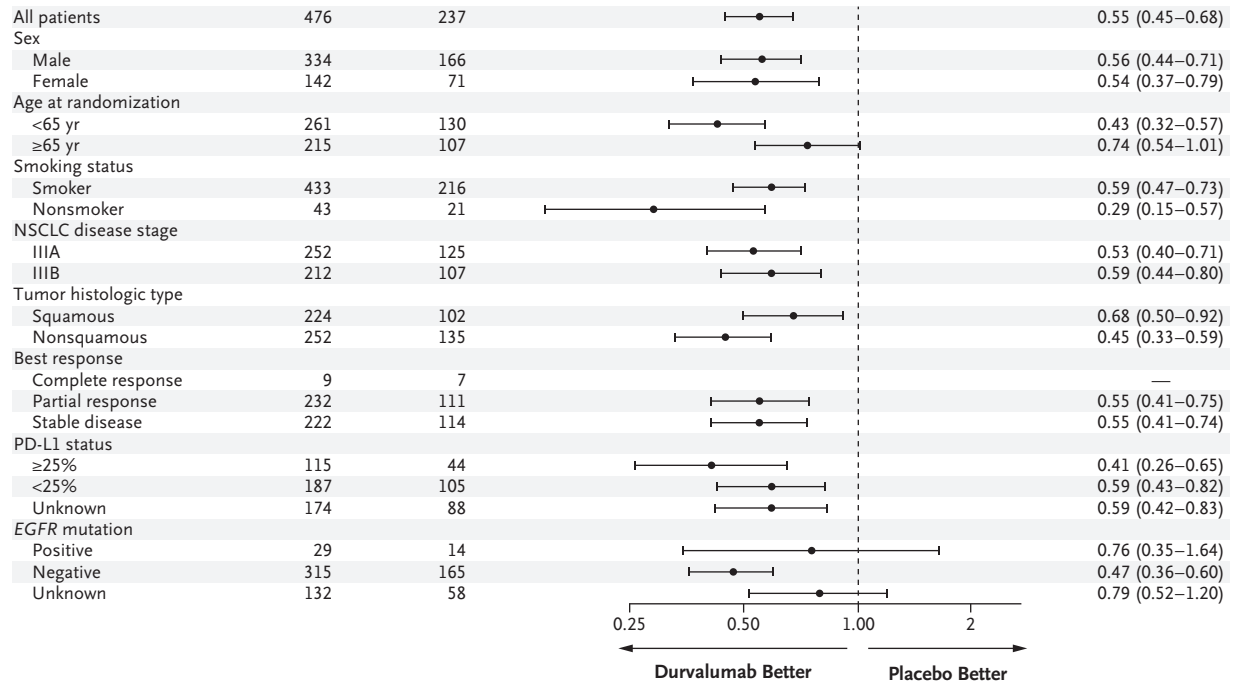

Figure 2. Subgroup Analysis of Prognostic Factors for Progression-free Survival in the Intention-to-Treat Population.

Progression-free survival was defined according to RECIST, version 1.1, and assessed by means of blinded independent central review. The hazard ratio and 95% confidence interval were not calculated for the complete response because this subgroup had less than 20 events. EGFR denotes epidermal growth factor receptor, and PD-L1 programmed death ligand 1.

(Table 3); grade 3 or 4 adverse events occurred in 29.9% and 26.1%, respectively. The most common grade 3 or 4 adverse event was pneumonia (in 4.4% of patients in the durvalumab group and 3.8% of patients in the placebo group). Discontinuation due to adverse events occurred in 15.4% of patients in the durvalumab group and 9.8% of patients in the placebo group, and serious adverse events occurred in 28.6% and 22.6%, respectively (Table S7 in the Supplementary Appendix). Death due to adverse events occurred in 4.4% of patients in the durvalumab group and 5.6% of patients in the placebo group (Table 3). Treatment-related adverse events are summarized in Table S8 in the Supplementary Appendix.

The most frequent adverse events leading to discontinuation of durvalumab and placebo were pneumonitis or radiation pneumonitis (in 6.3% and 4.3%, respectively) and pneumonia (in 1.1% and 1.3%). In patients who received durvalumab, as compared with those who received placebo, pneumonitis or radiation pneumonitis of any grade occurred in 33.9% and 24.8% and pneumonitis or radiation pneumonitis of grade 3 or 4 occurred in 3.4% and 2.6%; pneumonia of any grade occurred in 13.1% and 7.7%, and pneumonia of grade 3 or 4 occurred in 4.4% and 3.8%.

Adverse events of any grade that were of special interest, regardless of cause, were reported in 66.1% of patients in the durvalumab group and 48.7% of patients in the placebo group. The majority were grade 1 or 2, and events of grade 3 or higher were infrequent (in <10% of patients) in both groups. The most frequent adverse events of any grade that were of special interest with durvalumab versus placebo were diarrhea (18.3% and 18.8%), pneumonitis (12.6% and 7.7%), rash (12.2% and 7.3%), and pruritus (12.2% and 4.7%). Adverse events of special interest for which patients received concomitant treatment were reported in 42.1% and 17.1% of patients, respectively; treatments included glucocorticoids (in 15.2% and

Table 2. Antitumor Activity in the Intention-to-Treat Population.*

Variable	Durvalumab (N=443)†	Placebo (N=213)†	Treatment Effect‡	P Value
Objective response				
No. of patients with response	126	34		
% of patients (95% CI)	28.4 (24.3–32.9)	16.0 (11.3–21.6)	1.78 (1.27–2.51)	<0.001
Best overall response — no. (%)§				
Complete response	6 (1.4)	1 (0.5)		
Partial response	120 (27.1)	33 (15.5)		
Stable disease	233 (52.6)	119 (55.9)		
Progressive disease	73 (16.5)	59 (27.7)		
Could not be evaluated	10 (2.3)	1 (0.5)		
Duration of response — mo				
Median	NR	13.8	0.43	
95% CI		6.0–NR	0.22–0.84	
Ongoing response at data cutoff point — %¶				
At 12 mo	72.8	56.1		
At 18 mo	72.8	46.8		

* The tumor response was assessed by means of blinded independent central review. NR denotes not reached.
† The analysis was performed with data from patients with measurable disease at baseline as determined by either of the two independent central reviewers.
‡ The relative risk (95% CI) is shown for the objective response rate, and the hazard ratio (95% CI) is shown for the duration of response. Placebo was the reference group when relative risk and hazard ratio were calculated; therefore, a relative risk greater than 1 is in favor of durvalumab and a hazard ratio less than 1 is in favor of durvalumab.
§ One patient could not be included in any of the best-overall-response categories because of inconsistency in the baseline assessment for measurable disease between the two independent central reviewers.
¶ Percentages were calculated with the use of the Kaplan–Meier method.

6.8%), high-dose glucocorticoids (8.8% and 5.1%), endocrine therapy (11.6% and 1.3%), and other immunosuppressive agents (0.4% of both groups).

Immune-mediated adverse events of any grade, regardless of cause, were reported in 24.2% of patients in the durvalumab group and 8.1% of patients in the placebo group; grade 3 or 4 immune-mediated adverse events were reported in 3.4% and 2.6% of patients, respectively (Table S9 in the Supplementary Appendix). Treatments for immune-mediated adverse events included systemic glucocorticoids (in 14.3% of patients in the durvalumab group and 5.6% in the placebo group), high-dose glucocorticoids (8.2% and 4.3%), endocrine therapy (10.7% and 1.3%), and other immunosuppressive agents (0.4% of both groups).

DISCUSSION

In the planned interim analysis of the PACIFIC study, the coprimary end point of progression-free survival was met. Among patients with locally advanced, unresectable NSCLC, progression-free survival was 11 months longer among patients who received durvalumab than among those who received placebo (hazard ratio for disease progression or death, 0.52; P<0.001). The longer progression-free survival was accomplished in a biomarker-independent population. Patients with a level of PD-L1 expression on tumor cells of less than 25% accounted for a larger proportion of participants in this study than patients with 25% or greater PD-L1–positive tumor cells. In addition, the difference in progression-free survival in favor of durvalumab was shown across all prespecified subgroups, including patients who were not expected to have a response according to the results of trials involving patients with advanced or metastatic disease.

Although data on overall survival were immature at the time of this analysis, clinical benefit with durvalumab was evident by improve-

Table 3. Adverse Events of Any Cause.

Event	Durvalumab (N=475)		Placebo (N=234)	
	Any Grade*	Grade 3 or 4	Any Grade*	Grade 3 or 4
	number of patients with event (percent)			
Any event	460 (96.8)	142 (29.9)	222 (94.9)	61 (26.1)
Cough	168 (35.4)	2 (0.4)	59 (25.2)	1 (0.4)
Pneumonitis or radiation pneumonitis†	161 (33.9)	16 (3.4)	58 (24.8)	6 (2.6)
Fatigue	113 (23.8)	1 (0.2)	48 (20.5)	3 (1.3)
Dyspnea	106 (22.3)	7 (1.5)	56 (23.9)	6 (2.6)
Diarrhea	87 (18.3)	3 (0.6)	44 (18.8)	3 (1.3)
Pyrexia	70 (14.7)	1 (0.2)	21 (9.0)	0
Decreased appetite	68 (14.3)	1 (0.2)	30 (12.8)	2 (0.9)
Nausea	66 (13.9)	0	31 (13.2)	0
Pneumonia	62 (13.1)	21 (4.4)	18 (7.7)	9 (3.8)
Arthralgia	59 (12.4)	0	26 (11.1)	0
Pruritus	58 (12.2)	0	11 (4.7)	0
Rash	58 (12.2)	1 (0.2)	17 (7.3)	0
Upper respiratory tract infection	58 (12.2)	1 (0.2)	23 (9.8)	0
Constipation	56 (11.8)	1 (0.2)	20 (8.5)	0
Hypothyroidism	55 (11.6)	1 (0.2)	4 (1.7)	0
Headache	52 (10.9)	1 (0.2)	21 (9.0)	2 (0.9)
Asthenia	51 (10.7)	3 (0.6)	31 (13.2)	1 (0.4)
Back pain	50 (10.5)	1 (0.2)	27 (11.5)	1 (0.4)
Musculoskeletal pain	39 (8.2)	3 (0.6)	24 (10.3)	1 (0.4)
Anemia	36 (7.6)	14 (2.9)	25 (10.7)	8 (3.4)

* Included are events that were reported in at least 10% of the patients in either group. Grade 5 adverse events of any cause occurred in 21 patients (4.4%) who received durvalumab (4 [0.8%] with pneumonitis, 2 [0.4%] with cardiac arrest, and 1 each [0.2%] with the following: pneumonia, bacterial pneumonia, pneumococcal pneumonia, sepsis, septic shock, cardiomyopathy, cardiopulmonary failure, myocardial infarction, aortic dissection, dyspnea, emphysema, hemoptysis, respiratory distress, respiratory failure, radiation pneumonitis, right ventricular failure, increased level of brain natriuretic peptide, and unknown cause). Grade 5 adverse events of any cause occurred in 13 patients (5.6%) who received placebo (3 each [1.3%] with pneumonitis and pneumonia and 1 each [0.4%] with the following: pneumonia streptococcal, West Nile virus infection, cardiac arrest, eosinophilic myocarditis, hemoptysis, intestinal obstructions, radiation pneumonitis, and unknown cause). Each patient could have had more than one grade 5 adverse event.

† Pneumonitis or radiation pneumonitis was assessed by investigators with subsequent review and adjudication by the study sponsor. In addition, pneumonitis is a grouped term that includes acute interstitial pneumonitis, interstitial lung disease, pneumonitis, and pulmonary fibrosis.

ment in all secondary end points, such as an objective response rate that was higher by 12.4 percentage points with durvalumab than with placebo (P<0.001). In addition, responses with durvalumab were durable as compared with placebo (72.8% of patients who had a response to durvalumab had an ongoing response at both 12 and 18 months as compared with 56.1% and 46.8%, respectively, who had a response to placebo). Durvalumab also had a favorable effect on the frequency of new metastases, including a lower incidence of new brain metastases.

The safety profile of durvalumab in this population was consistent with that of other immunotherapies and with its known safety profile as monotherapy in patients with more advanced disease (stage IIIB or IV NSCLC).[18] Although the incidences of some adverse events of any cause, including pneumonitis or radiation pneumonitis, were increased with both durvalumab and

placebo in this study, this was expected after definitive chemoradiotherapy. In addition, pneumonitis or radiation pneumonitis in patients who received durvalumab was mostly low grade, and the incidence of clinically important grade 3 or 4 events was well balanced between the groups (3.4% in the durvalumab group and 2.6% in the placebo group) and lower than that in other studies in the same disease context.[6,24] Taken together, these data suggest that durvalumab has manageable side effects after chemoradiotherapy.

In conclusion, in the PACIFIC study, one of the coprimary end points was met at this planned interim analysis, and this study showed a significant increase in progression-free survival and no new safety signals with durvalumab in patients with stage III, unresectable NSCLC who had received chemoradiotherapy. These positive findings in an unselected patient population, irrespective of baseline expression of PD-L1 on tumor cells, suggest that durvalumab may be an effective adjuvant therapy in patients with stage III disease after standard treatment. Uncertainty about the potential mechanisms driving the interaction between immunotherapy and chemoradiotherapy warrants further investigation.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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